SUMMARY OF CHANGES

Date: February 20, 2017

Document: NCI Protocol #9653, PhII-130: "Phase II Trial of Gemcitabine-Eribulin (GE) in Cisplatin Ineligible Patients with Advanced or Unresectable Urothelial Carcinoma of the Bladder."

Note: The following is a Summary of Changes between the 5.2.16 and 2.20.17 versions of protocol

Section	**Description of Change (v. 5.2.16 and v. 2.20.17)**
Face page	• Changed protocol version and headers to February 20, 2017 • Removed P2C-IL07
TOC	Updated page numbers
4.2	Updated verbiage per current CTEP template.
8.1	Added section 8.1.2.3 - Investigator Brochure information. Added section 8.1.2.4 – Useful links and contacts
12	Revised this section in accordance with recent changes to the ETCTN template language. 12.1.1 – Updated CTMS language per CTEP 12.1.2 – Removed CDUS language as study is using CTMS 12.2 – Deleted the section as multicenter guidelines do not apply to ETCTN trials
13	Updated the statistics to state: Study enrollment will be extended if the following 2 conditions hold: (1) 7 or more patients of the 21 eligible patients experience a CR or PR, AND (2) there are patients who failed to receive 2 courses of treatment and undergo radiographic evaluation of tumor burden after the 2nd course for reasons be unrelated to disease progression. Thus accrual will be extended to "replace" patients who terminated treatment early for reasons of adverse events or toxicity or decisions unrelated to disease progression; patients who fail to receive 2 courses because of early progression will not be "replaced". Although all eligible patients who begin treatment will be included in the primary analysis, this extension will permit an estimate of the response rate in those patients who could receive 2 courses of therapy.
Appendix B	Deleted this Appendix as multicenter guidelines do not apply to ETCTN trials.

NCI Protocol #: 9653

Local Protocol #: PhII-130

TITLE: Phase II Trial of Gemcitabine-Eribulin (GE) in Cisplatin Ineligible Patients with Advanced or Unresectable Urothelial Carcinoma of the Bladder

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LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
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NCI-Supplied Agent(s): E7389 (Halichondrin B Analog) eribulin (NSC 707389)

Other Agent(s): Gemcitabine (Gemzar™), Lilly Oncology

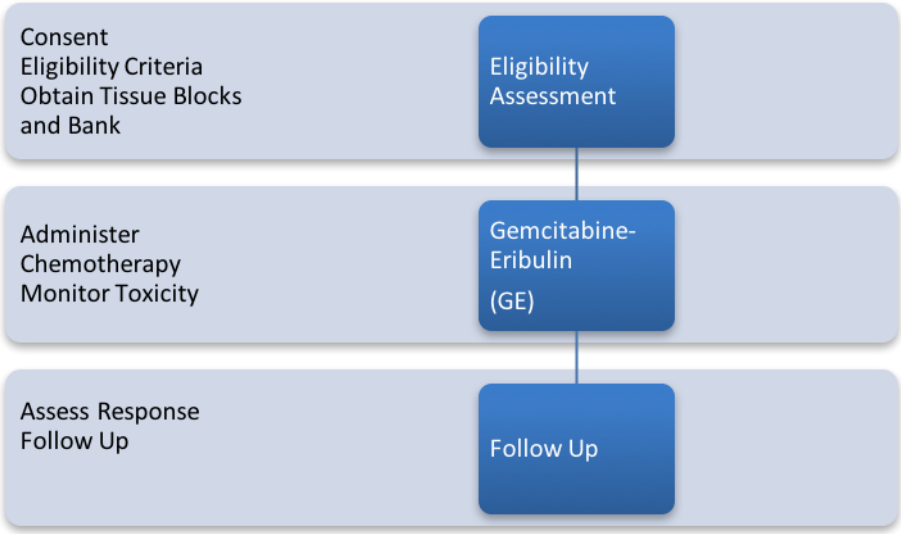
IND #: 64395

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

May 27, 2014	Initial Protocol
July 10, 2014	Consensus Review
August 4, 2014	Follow Up Review
August 14, 2014	Follow Up Review
September 24, 2014	Amendment
May 11, 2015	Amendment
February 8, 2016	Amendment
February 25, 2016	Amendment
May 2, 2016	Amendment – RRA
February 20, 2017	Amendment

SCHEMA


Consent
Eligibility Criteria
Obtain Tissue Blocks
and Bank
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Assessment
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Assess Response
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Follow Up

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1. OBJECTIVES

This is a phase II clinical trial of eribulin given with gemcitabine in patients with advanced or unresectable urothelial carcinoma who have not received any prior chemotherapy for the advanced disease and who are not eligible to receive cisplatin-based chemotherapy.

1.1 Primary Objective

The primary objective of this study is to estimate the objective response rate of gemcitabine-eribulin (GE) when given to cisplatin ineligible patients with advanced or unresectable urothelial carcinoma who have not received any prior chemotherapy for the advanced disease. Objective response is defined as either a complete response (CR) or a partial response (PR) based on RECIST v1.1.

1.2 Secondary Objectives

The secondary objectives are (1) to estimate the median progression-free survival (PFS), and (2) to summarize the toxicity profile (using CTCAE v4 criteria) of the GE regimen in these patients.

2. BACKGROUND

2.1 Study Disease(s)

Urothelial carcinoma of the bladder remains one of the most challenging and lethal urologic cancers. It is the second most common genitourinary (GU) cancer next to prostate cancer with a 2013 estimated incidence of 72,570 (69,250 in 2011) and has risen to be the second most deadly GU cancer with 15,210 estimated deaths in 2013 (14,990 estimated bladder cancer deaths in 2011)[1,2]. Many of these patients will have superficial disease at diagnosis (75-80%); however, approximately two thirds of those who present with muscle invasion will go on to develop regional or systemic disease. Despite improvements in surgical techniques and multimodal therapy, 5-year survival rates for patients with invasive bladder cancer remain suboptimal [3]. Virtually all deaths from bladder cancer result from muscle invasive disease that recurs or metastasizes after local therapy[4].

Platinum-based regimens are the mainstay of treatment for recurrent or metastatic bladder cancer[5]. The MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) regimen has produced response rates of 40 to 70% with 13 to 28% of patients having complete responses in Phase II and III trials[6,7]. The gemcitabine-cisplatin (GC) doublet has shown a similar response rate and survival as the MVAC combination, but a reportedly better toxicity profile[7]. However, the median overall survival of patients treated with either regimen is still only between 12 and 14 months and less than 10% of patients become long term disease-free survivors[7-10].

In addition, patients affected with this disease are often elderly and have multiple comorbid conditions such as renal insufficiency and congestive heart failure, which preclude them from receiving platinum-based therapy. It is estimated that 50% of patients are cisplatin-ineligible due to renal function impairment, compromised performance status, and/or comorbid conditions (such as congestive heart failure, among others) preventing them from receiving high volume hydration[11]. While it is less clear what precise proportion of the cisplatin-ineligible patients have

renal impairment as the sole reason for ineligibility, data from the adjuvant setting (i.e., patients fit enough to undergo radical surgery) suggest that between 25-50% of patients had a creatinine clearance of <60ml/min depending on the formula used for calculation and up to 40% of patients over 70 years of age using Cockroft-Gault formula[12]. Thus, there is an unmet medical need for treatment in patients who have significant comorbidities, particularly renal dysfunction.

Although the use of taxane combinations has been explored by ECOG as a first line alternative in patients with renal dysfunction, but there is still no widely accepted standard of care. There still is an ongoing need for the development of active agents to fill this void. Eribulin is a notable candidate to fulfill this role, given its reliance principally on hepatic metabolism and its promising single agent activity in early clinical trials[13].

2.2 Eribulin E7389

Halichondrin B is a potent antimitotic agent due to its inhibition of tubulin polymerization and microtubule assembly. It has remarkable *in vitro* and *in vivo* activity in a number of human tumor models, including melanoma, osteogenic sarcoma, lung and colon cancer[14,15].
Of the 180 compounds that were screened, eribulin (previously E7389, ER 086526, and NSC-707389) was shown to retain significant in vitro as well as in vivo efficacy in a variety of human tumor xenograft models, including breast, colon, melanoma and ovarian cancer models[16]. Eribulin showed sub-nM in vitro growth inhibition against several human cancer cell lines and was found to induce a G_2-M cell cycle arrest in association with the disruption of mitotic spindles[17]. Further studies showed that prolonged mitotic blockage by eribulin led to apoptotic cell death in cancer cells in vitro[18]. The studies in xenograft models demonstrated 20-100 fold potency of eribulin when compared to paclitaxel, with frank regressions and increased lifespans shown in the mice, together with a significantly wider therapeutic window[17]. In vivo activity was found to be schedule dependent, with intermittent dosing demonstrating the best antitumor efficacy and also the least toxicity[19].

In light of this very promising anticancer activity, preclinical studies with eribulin were undertaken in rats and dogs. These studies showed that eribulin exhibits rapid and extensive tissue distribution in rats and dogs with an extended terminal $t_{1/2}$ and that it does not bind strongly to plasma protein. Reversible bone marrow suppression was the dose-limiting toxicity in both rats and dogs[20].

Three phase I and two phase II trials with eribulin are ongoing or have completed accrual. In a CTEP sponsored phase I trial conducted by the California Cancer Consortium, eribulin was given as a weekly bolus intravenous injection three weeks out of four, starting at 0.125 mg/m^2/wk. The first part of the trial was a rapid escalation phase, which ended with a grade 3 alkaline phosphatase elevation at 0.5 mg/m^2/wk. The second part of the trial consisted of a standard 3x3 dose escalation, which ended at 2.0 mg/m^2/wk with one grade 3 febrile neutropenia and one grade 4 neutropenia. The MTD was 1.4 mg/m^2/wk. Non-hematological toxicities included hypoglycemia, hypophosphatemia and fatigue. Of 38 evaluable patients who had refractory or advanced solid tumors, two had a partial response (one bladder, see below), three had minor responses and twelve had stable disease lasting a median of 4 months (range 2-14)[13]. Of these, three patients had heavily pretreated bladder cancer. One experienced a partial response and the other two had stable disease for 24 weeks.

The pharmacokinetic studies undertaken in this study demonstrated tri-phasic elimination with a rapid distributive phase followed by a prolonged elimination from plasma resulting in a terminal $t_{1/2}$ of 36-48 hours. At the MTD, plasma levels remained at concentrations (median of 0.8 nM, range 0.2- 2.5 nM) well above those required for in vitro toxicity for more than one week. A small fraction of drug (< 10%) was excreted unchanged into the urine and no circulating metabolites were detected[13].

The two Eisai-sponsored trials are looking at different schedules of administration of a 1-hour intravenous infusion of eribulin. In one, the drug is given weekly for three weeks out of four (study #101), and in the other the drug is given once every three weeks (study #102). Twenty-six patients have been enrolled to the first study (#101), with doses ranging from 0.5 to 2.8 mg/m^2. Grade 3 neutropenia and grade 3 fatigue were reported at the 0.5 mg/m^2 dose level but the MTD for this schedule has not been reported[21]. Eighteen patients have been enrolled to the second study (#102), with doses ranging from 0.25 to 4 mg/m^2. Neutropenia was found to be the dose-limiting toxicity in this study, with the MTD expected to be at 2mg/m^2 on this schedule. Four patients have had stable disease for more than 4 cycles[22]. The pharmacokinetic analyses conducted in these studies also confirmed a rapid distribution and a prolonged elimination phase[23]. The two Eisai-sponsored phase II trials in breast and lung cancer that are ongoing are evaluating the 1.4 mg/m^2/wk dose administered as an intravenous bolus for three out of every four weeks. Accrual to these trials is ongoing but the safety data collected up until this point suggests that dosing 2 weeks out of every 3 weeks is more tolerable than dosing 3 out of every 4 weeks. Based on these data, Eisai has recommended that a day 1 and 8 dosing every 21 days be used instead of the day 1, 8 and 15 dosing every 28 days, in future studies.

Most recently, a CTEP sponsored phase I trial of GE demonstrated safety of the combination at 1000 mg/m^2 of gemcitabine and 1.4 mg/m^2, of eribulin where each of the agent was given on days 1 and 8 of a 21 day cycle[24]. More details on this study are discussed in 2.4.

2.3 Gemcitabine

Gemcitabine is a pyrimidine antimetabolite, 2'deoxy -2'difluoro-cytidine (gemcitabine) has been introduced into clinical practice for urothelial and a range of other tumors. In preclinical systems gemcitabine showed very significant activity against experimental solid tumors [25] and human tumor xenografts [26]. It is activated intracellularly to the triphosphate, 2'deoxy -2'difluoro-cytidine 5'-triphosphate (dFdCTP) and in this form is incorporated into DNA [27-29]. Gemcitabine entry to cells requires the presence of the nucleoside transporter system, with cells deficient in this transporter being gemcitabine resistant [27]. The activity of gemcitabine is cell cycle specific with blockade at the G1/S phase transition, perhaps suggesting that RR inhibition is an important contributor to gemcitabine antineoplastic effect.

In the initial phase I clinical trial, the drug was given over a 30 minute infusion weekly for three weeks every four weeks. The maximum tolerated dose was 790 mg/m^2 with myelosuppression predominantly thrombocytopenia and anemia being the dose limiting toxicity [7,30]. However, subsequent studies have shown that considerably higher doses can be given safely, particularly to patients with little or no prior therapy. In patients with non-small cell lung cancer and no prior therapy, O'Rourke et al. found that 2500 mg/m^2 given over 4 hours every two weeks was below

the MTD [31]. Initial pharmacokinetic studies showed a rapid elimination of the drug with a median half life of eight minutes. The drug was rapidly converted to the corresponding uracil metabolite 2',2'-difluorodeoxyuridine which had a longer half life, with a median of 14 hours. Antitumor activity for gemcitabine against bladder cancer was noted in the phase I study by Pollera et al. in 14 patients receiving gemcitabine at doses greater than 875 mg/m^2, they observed 1 CR and 2 PR [32]. A response rate of 28% was observed in a phase II trial in previously untreated patients with bladder cancer [33]. Subsequently, the combination of gemcitabine and cisplatin was assessed in a phase II trial with a response rate of 41% [34]. This combination was then compared to MVAC in a randomized phase III trial and found to produce equivalent response and survival with better quality of life [7]. De Mulder et al. noted response rate of 8.1% or 3 of 39 evaluable patients in a phase II study of gemcitabine in renal cell carcinoma, with durable responses exceeding 12 months in 2 patients [35].

Gemcitabine is part of most combination regimens for urothelial cancer including MVAC[36,37], GC[7], PGC[38] and MCAVI[11] as well as single agent[39] and as will be discussed was tried in combination with eribulin in a CTEP sponsored trial- see 2.4.

2.4 Rationale

Based on the preliminary evidence of clinical activity of eribulin in metastatic urothelial carcinomas, we propose a phase II study of this drug given at a dose of 1.4 mg/m^2 in combination with gemcitabine 1000mg/m^2 on days 1 and 8 of a 21 day cycle in patients with metastatic or unresectable urothelial carcinoma of the bladder who are not candidates for cisplatin therapy.

Eribulin is metabolized primarily in the liver and no renal toxicity has been observed in the phase I studies performed with this agent to-date, therefore, we expect eribulin to be well-tolerated in patients with renal dysfunction at the MTD previously defined for patients with normal renal function (i.e. 1.4 mg/m^2/week). Gemcitabine can be given at full doses to patients with a CrCl > 30ml/min.

The Phase II study of single agent eribulin in first line advanced urothelial cancer patients was completed and presented at ASCO 2010 with a response rate of 38%, median TTP 3.9 months and median OS 9.4 months[40]. This compares favorably with prior single agent activity for drugs that are standard of care for urothelial cancer, for example with gemcitabine: response rate 22.5-28% and overall survival 5-12.5 months, and cisplatin: response rate 12% and overall survival 8.2 months[33,37,39].

The phase I study in renal impaired patients was also presented at ASCO 2010 suggesting that full dosing of eribulin is feasible and efficacious in patients with creatinine clearance values down to 20 mL/min[41]. Eribulin also has significant activity in patients who have progressed after platin regimens for advanced or metastatic disease. In a recent NCI-CTEP sponsored phase II study of eribulin in platinum-treated tubulin naive advanced urothelial cancer, overall RR was 36% (95%CI: 21, 53%), including 1 CR, 7 PR, and 6 unconfirmed PR. [Confirmed RR was 21% (95%CI: 9, 36%)]. Stable disease for ≥12 weeks was seen in 12 patients (31%). PD was best response in 11 patients (28%). At median follow-up of 5.9 (1.4, 17.1) months, median PFS was 4.1 months (2.6, 6.4). Median OS was 9.6 months (5.3, ∞) (16 patients died). PFS was associated

with Bajorin risk group (p=0.005 for trend). Toxicities included grade 3/4 neutropenia (24), grade 3 febrile neutropenia (3), grade 1/2 sensory neuropathy (14), grade 3 hyperglycemia (1), grade 1 hyponatremia (8), grade 1/2 alopecia (16), grade 1 leg fatigue & aching (2)[42].

Most recently a CTEP-sponsored phase I dose escalation trial of GE has been conducted which tested four dose levels of this doublet. Gemcitabine-Eribulin doses were as follows: 800-0.7, 1000-0.7, 1000-1.0 and 1000-1.4 mg/m^2. Safety for the highest dose level was established and evidence of antitumor activity for this regimen was seen[24]. A summary of the findings in this trial is provided courtesy of Dr. Rakesh Goel from the Ottawa Hospital (personal communication)[24]. In this trial, 45 patients were included in the study in 3 cohorts: pretreated (n=21), gynecologic cancers expansion cohort (n=10), and chemo-naïve (n=14). The initially planned Day 1, 8, and 15 in a 28 day cycle was not tolerated at dose level 1 and therefore remainder of the trial used a 21 day schedule with treatment on days 1 and 8. The most common grade 3-4 toxicities included: neutropenia (24), leukopenia (16), lymphopenia (12), ALT rise (7), fatigue (7), AST rise (5), thrombocytopenia (4), anemia, diarrhea, nausea, and vomiting (2 each). Non-hematological toxicities and specifically neuropathy were minimal. Efficacy assessments showed evidence for anti-tumor activity in each of the pre-defined cohorts. In the pretreated cohort, disease control rate (DCR) was 48% (SD 8, PR 2, PD 7, inevaluable 4, n=21). In the gynecologic cancers expansion cohort, DCR was 80%, including 9 ovarian cancers (SD 6, PR 1, PD 2) and 1 endometrial cancer with SD. In the chemo-naïve cohort, DCR was 57% (SD 8, PR 2, PD 3, inevaluable 1).

Eribulin is approved by the FDA for use in metastatic breast cancer previously treated with chemotherapy after demonstrating an overall survival advantage over physicians' choice in the EMBRACE trial[43].

2.5 Correlative Studies Background

N/A

3. PATIENT SELECTION

3.1 Eligibility Criteria

This trial is open to cisplatin-ineligible patients with advanced or unresectable urothelial carcinoma who have not received any prior chemotherapy for advanced disease.

3.1.1 Patients must have locally advanced or metastatic predominantly urothelial carcinoma of the bladder, ureter, or urethra that is not amenable to curative surgical treatment.

3.1.2 Patients must have histologically confirmed predominantly urothelial carcinoma of the bladder, ureter, or urethra.

3.1.3 Patients must have measurable disease per RECIST 1.1 criteria , defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.4 Patients must be ineligible for treatment with cisplatin, based on one of:

- Calculated creatinine clearance (CrCl) ≥ 30 and <60 mL/min (Cockcroft-Gault)
- CTCAE Gr ≥ 2 hearing loss
- CTCAE Gr ≥ 2 neuropathy

3.1.5 Patients must not have received prior systemic therapy for their advanced cancer. Prior intravesical therapy completed 4 weeks prior to enrollment and adjuvant/neoadjuvant chemotherapy completed more than 6 months prior to diagnosis of advanced disease are permitted.

3.1.6 Patients must be 18 years of age or older. Because no dosing or adverse event data are currently available on the use of eribulin in combination with gemcitabine in patients <18 years of age, children are excluded from this study. In addition, urothelial cancer of the bladder is extremely rare in pediatric patients.

3.1.7 Zubrod performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.8 Life expectancy of greater than 3 months

3.1.9 Patients must have adequate organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	< 1.5 times the upper limit of normal (x ULN) for the institution
– AST(SGOT)/ALT(SGPT)	≤3 × institutional upper limit of normal
– creatinine clearance	calculated creatinine clearance (CrCl) ≥ 30 mL/min and <60 mL/min (Cockroft-Gault) unless the patient qualified based on hearing loss or neuropathy (see 3.1.4)

3.1.10 The effects of gemcitabine and eribulin on the developing human fetus are unknown. For this reason and because *tubulin inhibiting* agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of gemcitabine and eribulin administration.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients with a small cell component in their histology are excluded.

3.2.2 Patients who have had chemotherapy for the treatment of the advanced or unresectable urothelial cancer of the bladder are not eligible; patients who were previously treated for local disease must not have received radiotherapy or chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study and must have recovered from adverse events due to agents administered more than 4 weeks earlier. Patients who have received neoadjuvant or adjuvant chemotherapy must have completed treatment at least 6 months prior to diagnosis of metastatic disease.

3.2.3 Patients who are receiving any other investigational agents.

3.2.4 Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

3.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to gemcitabine and eribulin.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, a second cancer diagnosis within the past 5 years, or a cancer undergoing any treatment, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study because eribulin is an anti-tubulin agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with eribulin and gemcitabine, breastfeeding should be discontinued if the mother is treated with eribulin and gemcitabine.

3.2.8 Human immunodeficiency virus (HIV)-positive patients with inadequate CD4 counts or those who are on combination antiretroviral therapy with strong CYP3A4 effects are ineligible for this trial

3.2.9 QT prolongation has been observed in patients that received Eribulin and therefore:

- Patients with baseline QTc prolongation greater than grade 1 are excluded from this study. Patients with grade 1 QTc elevation are eligible but must be monitored with ECG (EKG) exams, for the first 3 cycles of treatment. Eribulin time to Cmax after infusion is about 10 minutes, and half life is 40 minutes[44]. ECG (EKG) should be performed between 10 to 40 minutes after eribulin administration (on day 1 and day 8 of treatment). Continued ECG (EKG) monitoring beyond cycle 3 can be done at the discretion of the treating physician.
- Patients with congenital long QT syndrome are excluded from this study.
- Other medications known to prolong QT interval should be discontinued and if not possible, patient is excluded from this study. Refer to http://crediblemeds.org for lists of drugs that may cause QT prolongation.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

4.1.1 CTEP Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at pmbregpend@ctep.nci.nih.gov.

4.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account is needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, and is critical to the conduct of this study, including document access, patient enrollment, and clinical data submission.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov.

4.1.3 For Questions and Support

For questions about Investigator Registration, please contact the CTEP Investigator Registration Help Desk: pmbregpend@ctep.nci.nih.gov.

For questions about Associate Registration or CTEP-IAM Account Creation, please contact the CTEP Registration Help Desk: ctepreghelp@ctep.nci.nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to: an active Federal Wide

Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the NCI# 9653 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the ETCTN link to expand, then select Phase 1 Grants followed by LAO-CA043, and protocol #9653
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will automatically load to RSS.)

4.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

ONLINE: www.ctsu.org (members' section) → Regulatory Submission Portal

4.2.3 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

• Site staff with the appropriate roles will reserve slots using IWRS (https://open.ctsu.org/).
• City of Hope Cancer Center will receive notification via the IWRS when a slot has been reserved. An email will be sent from the City of Hope Cancer Center to the site requesting further information such as: the patient initials, tumor type and potential start date. The spot will show as 'pending approval' in the system until the site sends a REGISTRATION FORM/ELIGIBILITY CHECKLIST (see CTSU website) accompanied with the signed consent, baseline labs, pathology report, CT/x-ray reports to the City of Hope Cancer Center at ccc@coh.org for review and confirmation of eligibility.
• Once the Registration has been reviewed, the City of Hope Cancer Center will either approve or disapprove the request depending on confirmation of patient eligibility. If approved, the City of Hope Cancer Centre will update the spot to 'reserved' in IWRS.
• The site can now enroll the patient into the study in OPEN
* At the time of registration the treatment arm will be randomly assigned

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the CTSU web site as a tool to verify eligibility.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://theradex.com/CTMS/Downloads.aspx. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7802 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator (cccp@coh.org) should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential

risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 Gemcitabine and Eribulin
Gemcitabine should be administered before Eribulin.

5.1.1.1 Eribulin (E7389) Administration

Eribulin will be administered on an outpatient basis after gemcitabine as an intravenous bolus over 2-5 minutes, once a week for two weeks in a row (on Days 1 and 8) of a 21 day cycle. The patient's starting dose will be 1.4 mg/m^2/week. The dose may be reduced for individual patients in subsequent cycles depending on toxicity (Section 6.2); there will be no intra-patient dose escalation.

Reported adverse events (AEs) and potential risks of eribulin are described in Section 7.1. Appropriate dose modifications for eribulin are described in Section 6.2. No investigational or commercial agents or therapies other than those described in Section 5 (Treatment Plan) may be administered with the intent to treat the patient's malignancy.

5.1.1.2 Gemcitabine Administration

Gemcitabine at a dose of 1000mg/m^2 will be administered intravenously over 30 minutes before eribulin once a week for two weeks in a row (on Day 1 and 8) of a 21 day cycle.

The patient's starting dose will be 1000 mg/m^2/week. The dose may be reduced for individual patients in subsequent cycles depending on toxicity (Section 6.2); there will be no intra-patient dose escalation.

Reported adverse events (AEs) and potential risks of gemcitabine are described in Section 0. Appropriate dose modifications for gemcitabine are described in Section 6.2. No investigational or commercial agents or therapies other than those described in Section 5.0 (Treatment Plan) may be administered with the intent to treat the patient's malignancy.

5.2 General Concomitant Medication and Supportive Care Guidelines

Prophylactic antiemetic therapy will be given as per institutional policy.

Erythropoietin may be administered for anemia/fatigue at the investigators' discretion, however prophylactic use of granulocyte/platelet colony stimulating factors is not permitted. If the patient experiences febrile neutropenia as a documented toxicity on this study then granulocyte colony stimulating factors may be used in line with institutional and ASCO guidelines.

Antidiarrheal medications, potentially including loperamide, along with supplemental fluids and other supportive measures are recommended at the discretion of the investigator.

All supportive measures consistent with optimal patient care will be given throughout the study. Patients should be cautioned about the concomitant use of cimetidine, trimethoprim, or other agents that interfere with creatinine secretion or the creatinine assay.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment with a 14 day delay in protocol scheduled treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

  Note: if a patient is to come off protocol apart from for disease progression then the treating physician should contact the study PI by email (sarmad.sadeghi@usc.edu).

5.4 Duration of Follow Up

Patients will be followed every 3 months for up to 36 months after end of treatment with gemcitabine and eribulin, until progression, start of a treatment with an agent other than gemcitabine or eribulin, of disease or death, whichever occurs first. In addition, patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event and will then be followed every 3 months, as above.

5.5 Criteria for Removal from Study

Patients will remain on-study for 36 months after going off treatment, progression of disease or initiation of new treatment, (whichever comes first) or at death or patient withdrawal of consent. The reason for study removal and the date the patient was removed must be documented in the Case Report Form. Every effort should be made to evaluate patients for a date and details of progression should they come off treatment for reasons other than progressive disease and in all cases for survival unless consent is specifically with drawn for that follow up.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Retreatment criteria and dosing delays

Prior to retreatment, patients must have recovered the following organ function:

- absolute neutrophil count ≥1,000/mm^3 (750/mm^3 for day 8)
- platelets ≥75,000/mm^3
- total bilirubin ≤ 1.5 institutional upper limit of normal (IULN)
- AST(SGOT)/ALT(SGPT) ≤ 3 X IULN
- Neuropathy Grade 0-1

Management of anemia (RBC transfusion, erythropoietin, etc) need not delay treatment at the discretion of the treating physician.

Fatigue and other laboratory and non-laboratory toxicities not listed above or under dose modifications (6.2, 6.3 and 6.4) may not require treatment delays and may be managed at the discretion of the treating physician.

Laboratory evaluations must be repeated within 24 hours prior to initiation of each cycle of therapy. Patients not fulfilling these criteria should have treatment delayed by 1 week to allow for recovery of organ function. Patients who cannot be retreated within 2 weeks of the originally scheduled Day 1 or Day 8 treatment should be removed from study.

Patients with grade 1 QTc elevation are monitored with ECG (EKG) examination after eribulin treatment between 10 to 40 minutes of completion of the eribulin on day 1 and day 8 treatments for the first 3 cycles of treatment. The expectation for QTc prolongation to manifest after 6 treatments with eribulin is low, and therefore continuation of ECG (EKG) monitoring for eribulin beyond the third cycle is left to the discretion of the treating physician. Patients with prolongation of QTc to grade 2 or greater should have ECG (EKG) undertaken at intervals until this resolves and have their ongoing involvement discussed with the study PI by email (sarmad.sadeghi@usc.edu).

6.2 Dose modifications for eribulin

If day 1 or day 8 dose of eribulin must be held for toxicities related to eribulin, day 1 or day 8 treatment (both eribulin and gemcitabine) will be held until toxicities resolve to a grade that would allow treatment to proceed. If patient cannot be treated (retreated) within 2 weeks of the originally scheduled Day 1 or Day 8 treatment, then treatment with eribulin will be discontinued.

- There will be no dose modifications for grade 1 or 2 toxicities that recover to a grade 0 or 1 or otherwise meet laboratory re-treatment parameters in 6.1 prior to the next cycle of treatment.

- If a patient experiences a grade 3 or 4 non-hematological toxicity attributable to eribulin, excluding:

- alopecia,
- hypersensitivity,
- nausea and vomiting that have not been treated with maximal antiemetic therapy or
- diarrhea that has not been treated with optimal antidiarrheal therapy

which resolves to a grade 0 or 1 prior to the next cycle of treatment, or within a ≤ 2 week delay, the patient may be retreated with eribulin at one dose level lower. If a lower dose is not possible due to a prior dose reduction, then treatment with eribulin will be discontinued.

- If a patient experiences a grade 3 or 4 hematological toxicity attributable to eribulin, excluding:
  - Leukopenia
  - Lymphopenia

  which resolves to a grade 0 or 1, prior to the next cycle of treatment, or within a ≤ 2 week delay, the patient may be retreated with eribulin one dose level lower or at the same level with G-CSF support based on the preference of the treating physician. If a lower dose is not possible due to a prior dose reduction, then treatment with eribulin will be discontinued.

- Patients who cannot be retreated within 2 weeks of the originally scheduled Day 1 or Day 8 treatment, he or she should have eribulin discontinued.

- No patient should have his/her eribulin dose re-escalated following dose reduction for toxicity.

Dose Level	***Eribulin* Dose**
Level 0	1.4 mg/m^2/week
Level -1	1.0 mg/m^2/week
Level -2	0.7 mg/m^2/week

6.3 Dose modifications for gemcitabine

- If gemcitabine is discontinued for any reason other than disease progression, patients may continue to receive eribulin. In cases of disease progression, combination treatment will be discontinued.

- Gemcitabine doses held on day 8 of a cycle where day 8 dose of eribulin is administered will not be made up at a later date.
- If more than one dose reduction applies, then use the lowest. Doses that are reduced at any point in a cycle will not be subsequently increased.
- If based on the criteria provided here a situation arises where because of toxicities gemcitabine dose is discontinued, treatment with eribulin alone shall be continued.

The following dose levels of gemcitabine will be used:

Dose Level	*Gemcitabine* Dose
Level 0	1000 mg/m^2/week
Level -1	750 mg/m^2/week
Level -2	500 mg/m^2/week

If further dose reductions are required, gemcitabine will be discontinued.

6.4 Dose Modifications for Eribulin and Gemcitabine for Nausea, Vomiting, Diarrhea, Neutropenia and Thrombocytopenia

Nausea	**Management/Next Dose for *Eribulin***	**Management/Next Dose for *Gemcitabine***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions for the same drug should go off protocol therapy.		
Recommended management: antiemetics.		

Vomiting	**Management/Next Dose for *Eribulin***	**Management/Next Dose for *Gemcitabine***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions for the same drug should go off protocol therapy.		
Recommended management: antiemetics.		

Diarrhea	**Management/Next Dose for *Eribulin***	**Management/Next Dose for *Gemcitabine***
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.

Diarrhea	**Management/Next Dose for *Eribulin***	**Management/Next Dose for *Gemcitabine***
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions for the same drug should go off protocol therapy.		
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.		

Neutropenia	**Management/Next Dose for *Eribulin***	**Management/Next Dose for *Gemcitabine***
≤ Grade 1 (≥ 1500)	No change in dose	No change in dose
Grade 2 (1000 to <1500)	No change in dose	No change in dose
Grade 3 (500 to <1000)	For Day 1: Hold* until neutrophil ≥ 1000. Resume at one dose level lower, if indicated.** For Day 8: Hold* until neutrophil ≥ 750. Resume at one dose level lower, if indicated.**	For Day 1: Hold* until neutrophil ≥ 1000. Resume at one dose level lower, if indicated.** For Day 8: Hold* until neutrophil ≥ 750. Resume at one dose level lower, if indicated.**
Grade 4 (<500)	For Day 1: Hold* treatment for one week and add GCSF. When neutrophils recover to Grade <4 treatment may continue according to the grade of residual neutropenia. GCSF should be added to the future cycles on Day 9. If neutrophils are still at grade 4 after one week of GCSF, patient will be removed from study. For Day 8: Hold* treatment for one week and add GCSF. When neutrophils recover to Grade <4 treatment may continue according to the grade of residual neutropenia. GCSF should	For Day 1: Hold* treatment for one week and add GCSF. When neutrophils recover to Grade <4 treatment may continue according to the grade of residual neutropenia. GCSF should be added to the future cycles on Day 9. If neutrophils are still at grade 4 after one week of GCSF, patient will be removed from study. For Day 8: Hold* treatment for one week and add GCSF. When neutrophils recover to Grade <4 treatment may continue according to the grade of residual neutropenia. GCSF should

Neutropenia	**Management/Next Dose for *Eribulin***	**Management/Next Dose for *Gemcitabine***
	be added to the future cycles on Day 9. If neutrophils are still at grade 4 after one week of GCSF, patient will be removed from study.	be added to the future cycles on Day 9. If neutrophils are still at grade 4 after one week of GCSF, patient will be removed from study.
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions for the same drug should go off protocol therapy.		

Thrombocytopenia	**Management/Next Dose for *Eribulin* (Dose reduction applicable only after *Gemcitabine* is discontinued§)**	**Management/Next Dose for *Gemcitabine***
≤ Grade 1 ≥75K)	No change in dose	No change in dose
Grade 2 (50K to <75K)	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3 (25Kto <50K)	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**
Grade 4 (<25K)	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**	Discontinue Gemcitabine
*Patients requiring a delay of >2 weeks should go off protocol therapy. **Patients requiring > two dose reductions for the same drug should go off protocol therapy. §Thrombocytopenia is more likely to be a toxicity of gemcitabine and gemcitabine dose reduction should occur first, if indicated.		

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting (via CTEP-AERS) **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2318 patients.* Below is the CAEPR for

Eribulin Mesylate (E7389; Halichondrin B Analog).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPR for E7389 (halichondrin B analog)

Version 2.6, March 23, 2016[1]

Adverse Events with Possible Relationship to Eribulin Mesylate (E7389; Halichondrin B Analog) (CTCAE 4.0 Term) [n= 2318]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Anal mucositis		***Anal mucositis (Gr 2)***
Constipation			***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 2)***
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
	Rectal mucositis		***Rectal mucositis (Gr 2)***
	Small intestinal mucositis		***Small intestinal mucositis (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection[2] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Dermatitis radiation		***Dermatitis radiation (Gr 2)***
	Radiation recall reaction (dermatologic)		***Radiation recall reaction (dermatologic) (Gr 2)***
INVESTIGATIONS			

Adverse Events with Possible Relationship to Eribulin Mesylate (E7389; Halichondrin B Analog) (CTCAE 4.0 Term) [n= 2318]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
	Platelet count decreased		***Platelet count decreased (Gr 3)***
	Weight loss		
White blood cell decreased			***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Hyperglycemia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Bone pain		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
	Paresthesia		
	Peripheral motor neuropathy		***Peripheral motor neuropathy (Gr 2)***
	Peripheral sensory neuropathy		***Peripheral sensory neuropathy (Gr 3)***
PSYCHIATRIC DISORDERS			
	Insomnia		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***

Adverse Events with Possible Relationship to Eribulin Mesylate (E7389; Halichondrin B Analog) (CTCAE 4.0 Term) [n= 2318]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia			***Alopecia (Gr 2)***
	Rash maculo-papular		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Muscle weakness includes Generalized muscle weakness, Muscle weakness left-sided, Muscle weakness lower limb, Muscle weakness right-sided, Muscle weakness trunk, and Muscle weakness upper limb under the MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS SOC.

Adverse events reported on Eribulin Mesylate (E7389; Halichondrin B Analog) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Eribulin Mesylate (E7389; Halichondrin B Analog) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (bone marrow failure); Blood and lymphatic system disorders - Other (febrile bone marrow aplasia); Blood and lymphatic system disorders - Other (pancytopenia); Hemolysis; Leukocytosis; Spleen disorder
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac arrest; Cardiac disorders - Other (cardiogenic shock); Cardiac disorders - Other (edema); Heart failure; Myocardial infarction; Palpitations; Pericardial effusion; Pericardial tamponade; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Eye disorders - Other (visual impairment); Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Bloating; Colitis; Colonic obstruction; Dry mouth; Duodenal fistula; Dyspepsia; Dysphagia; Enterocolitis; Esophageal stenosis; Gastric hemorrhage; Gastritis; Gastrointestinal disorders - Other

(abdominal hernia); Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (gastric pneumatosis); Ileus; Lower gastrointestinal hemorrhage; Oral dysesthesia; Oral hemorrhage; Oral pain; Pancreatitis; Rectal hemorrhage; Retroperitoneal hemorrhage; Small intestinal obstruction; Stomach pain; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Infusion site extravasation; Injection site reaction; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatic hemorrhage; Hepatic pain; Hepatobiliary disorders - Other (hepatitis)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Immune system disorders - Other (angioedema)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fracture; Gastric anastomotic leak; Vascular access complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased; Investigations - Other (blood chloride decreased); Investigations - Other (blood LDH increased); Investigations - Other (breath sounds abnormal); Investigations - Other (c-reactive protein increased); Investigations - Other (neutrophil count increased); Lipase increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Flank pain; Muscle weakness[3]; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS - Acoustic nerve disorder NOS; Ataxia; Depressed level of consciousness; Dysesthesia; Dysphasia; Edema cerebral; Encephalopathy; Hydrocephalus; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Neuralgia; Recurrent laryngeal nerve palsy; Reversible posterior leukoencephalopathy syndrome; Seizure; Sinus pain; Somnolence; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Renal and urinary disorders - Other (hemorrhage urinary tract); Renal calculi; Urinary retention; Urinary tract obstruction; Urinary tract pain; Urine discoloration
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Pelvic pain; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Hiccups; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Postnasal drip;

Productive cough; Pulmonary fibrosis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (asthma); Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease); Sore throat; Voice alteration; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Skin and subcutaneous tissue disorders - Other (skin exfoliation)
VASCULAR DISORDERS - Capillary leak syndrome; Hypertension; Hypotension; Lymphocele; Phlebitis; Superior vena cava syndrome; Thromboembolic event

Note: Eribulin Mesylate (E7389; Halichondrin B Analog) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Adverse Event List for Gemcitabine

>10%: Cardiovascular: Peripheral edema (20%), edema (13%) Central nervous system: Pain (10% to 48%), fever (30% to 41%), somnolence (5% to 11%) Dermatologic: Rash (24% to 30%), alopecia (15% to 18%), pruritus (13%) Gastrointestinal: Nausea/vomiting (64% to 71%; grades 3/4: 1% to 13%), constipation (10% to 31%), diarrhea (19% to 30%), stomatitis (10% to 14%) Hematologic: Anemia (65% to 73%; grade 4: 1% to 3%), leukopenia (62% to 71%; grade 4: ≤1%), neutropenia (61% to 63%; grade 4: 6% to 7%), thrombocytopenia (24% to 47%; grade 4: ≤1%), hemorrhage (4% to 17%; grades 3/4: <1% to 2%); myelosuppression is the dose-limiting toxicity Hepatic: Transaminases increased (67% to 78%; grades 3/4: 1% to 12%), alkaline phosphatase increased (55% to 77%; grades 3/4: 2% to 16%), bilirubin increased (13% to 26%; grades 3/4: <1% to 6%) Renal: Proteinuria (10% to 45%; grades 3/4: <1%), hematuria (13% to 35%; grades 3/4: <1%), BUN increased (8% to 16%; grades 3/4: 0%) Respiratory: Dyspnea (6% to 23%) Miscellaneous: Flu-like syndrome (19%), infection (8% to 16%; grades 3/4: <1% to 2%)

1% to 10%: Local: Injection site reactions (4%) Neuromuscular & skeletal: Paresthesia (2% to 10%) Renal: Creatinine increased (2% to 8%) Respiratory: Bronchospasm (<2%)

<1% (Limited to important or life-threatening; reported with single-agent use or with combination therapy, all reported rarely): Adult respiratory distress syndrome, anaphylactoid reaction, anorexia, arrhythmias, bullous skin eruptions, cellulitis, cerebrovascular accident, CHF, chills, cough, desquamation, diaphoresis, gangrene, GGT increased, headache, hemolytic uremic syndrome (HUS), hepatotoxic reaction (rare), hypertension, insomnia, interstitial pneumonitis, liver failure, malaise, MI, peripheral vasculitis, petechiae, pulmonary edema, pulmonary fibrosis, radiation recall, renal failure, respiratory failure, rhinitis, sepsis, supraventricular arrhythmia, weakness

Please refer the reader to the package insert(s) for the comprehensive list of adverse events

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

N/A

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

7.5 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 7.1.

8.1 CTEP IND Agent(s)

8.1.1 CTEP IND Agent - Eribulin - E7389 (NSC #707389)

Chemical Name: 11,15:18,21:24,28-Triepoxy-7,9-ethanol-12,15-methano-9*H*,15*H*-furo[3,2-*i*]furo[2',3':5,6]pyrano[4,3-*b*][1,4]dioxacyclopentacosin-5(4*H*)-one,2-[(2S)-3-amino-2-hydroxypropyl]hexacosahydro-3-methoxy-26-methyl-20,27-bis(methylene)-,(2*R*,3*R*,3a*S*,7*R*,8a*S*,9*S*,10a*R*,11*S*,12*R*,13a*R*,13b*S*,15*S*,18*S*,21*S*,24*S*,26*R*,28*R*,29a*S*)-methanesulfonate (salt)

Other Names: Halichondrin B analog, ER-086526, B1939, eribulin mesylate

Classification: Synthetic analog of the very rare marine sponge natural product, halichondrin B

Molecular Formula: $C_{40}H_{59}NO_{11}$ CH_4O_3S **M.W.:** 826.00

Approximate Solubility:
- Freely soluble in water, methanol, ethanol, 1-octanol, benzyl alcohol, dimethylsufoxide, *N*-methylpyrrolidone, dichloromethane and ethylacetate, and at pH 3-7.
- Soluble in acetone and at pH 9, and sparingly soluble in acetonitrile.
- Insoluble in *tert*-butylmethyl ether, *n*-heptane and *n*-pentane, but slightly soluble at pH 11

Mode of Action: Tubulin-binding agent (inhibition of microtubule polymerization)

How Supplied: E7389 is supplied by Eisai Medical Research Inc., and distributed by CTEP/NCI as 1 mg/vial (0.5mg/mL- 2mL fill). The clear, colorless, and sterile solution is packaged in 5 mL glass vial.

Component	Grade	Quantity per vial[a]
E7389[b]	Eisai Standard	1 mg
Ethanol	USP	0.1 mL
Hydrochloric acid	NF	Adjusting pH if needed
Sodium hydroxide	NF	Adjusting pH if needed
Water for Injection	USP	Qs to 2 mL

[a]Contain an excess of 0.26 mL with total drug content of 1.13 mg
[b]Anhydrous salt

Preparation: E7389 may be administered without further dilution or may be diluted in up to 100mL 0.9% Sodium Chloride Injection.

Storage: Store the intact vials as directed by the product label. Protection from light is not necessary.

Stability: Shelf-life surveillance of the intact vials is on-going.
- Undiluted E7389 solution (IV bolus) stored in a Polypropylene syringe is stable for 4 hours at ambient temperature and 24 hours at refrigerated temperature.
- E7389 diluted to a concentration between 0.02 mg/mL and 0.2 mg/mL in 0.9%

NaCl should not be stored longer than 24 hours at 2 to 8°C..

Route of Administration: Intravenous over 2-5 minutes.

Availability: E7389 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

E7389 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.2.3 Investigator Brochures - The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1.2.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: PMBRegPend@ctep.nci.nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://eapps-ctep.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
- IB Coordinator: IBCoordinator@mail.nih.gov

8.2 Gemcitabine

Product description and storage: (Gemzar®, Lilly Oncology) The gemcitabine will not be provided by the PMB and should be obtained from commercial sources. Gemcitabine is commercially available in vials containing either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment. The recommended diluent for reconstitution of gemcitabine is 0.9% Sodium Chloride Injection without preservatives. Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided. When prepared as directed, gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F). Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur. Please refer to the commercial package insert for complete drug information.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

While, for patients who consent, tissue from the diagnostic biopsy or prior TURBT or cystectomy will be collected and stored at a Biobank, no correlative studies are planned as part of this trial. However, patients can enroll in other non-therapeutic and biomarker clinical studies concurrently provided they do not require or suggest changes in therapy that are independent of progression criteria in this protocol.
The Biobank is being run by UC Davis Comprehensive Cancer Center and supported by the National Cancer Institute.

9.1 Collection of Specimens

Tumor specimens from the diagnostic biopsy should be submitted for banking along with a completed specimen submission form and a copy of the corresponding pathology report.

Ideally, 1-2 paraffin-embedded tissue blocks containing formalin-fixed tumor, processed according to standard institutional protocols, will be submitted. If blocks are unavailable, 10-15 unstained slides will be accepted as an alternative. Tissue should be cut at ~5 microns and mounted on positively charged (+) slides.

9.2 Shipping of Specimens

All archival paraffin block/slide specimens should be sent at ambient temperature. For summer shipments, please include a room temperature cool pack to insulate the specimen and protect the paraffin from melting. Specimens should be shipped to the following address:

Philip C Mack, PhD / Leslie Snyder-Solis
UCD Cancer Center
4501 X Street, Suite 1009
Sacramento, CA 95817

Phone: 916-734-6447
Email: ljsnyder@ucdavis.edu or pcmack@ucdavis.edu

Please notify the bank at the time of shipping via email (ljsnyder@ucdavis.edu).

9.3 Biomarker Studies

No biomarker studies are planned as part of this protocol. However, patients can enroll in other non therapeutic clinical trials.

10. STUDY CALENDAR

Baseline evaluations are to be conducted within 7 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Item	Pre-Study	Wk 1	Wk 2	Wk 3		Wk 4	Wk 5	Wk 6		Wk …	Wk …	Wk …	Off Study
		Cycle 1				**Cycle 2**				**Cycle …**			
Eribulin		X	X			X	X			X	X		
Gemcitabine		X	X			X	X			X	X		
Informed Consent	X												
Eligibility Assessment	X												
Demographics	X												
Concurrent Medications	X												
H&P	X	X				X				X			
Medication List	X	X				X				X			
Ht, Wt, BSA	X	X				X				X			
Vital Signs	X	X	X			X	X			X	X		
Performance Status	X	X				X				X			
CBC-Diff	X	X	X			X	X			X	X		
CMP†, LDH	X	X	X			X	X			X	X		
Creatinine Clearance calculation	X	X	X			X	X			X	X		
ECG (EKG) §	X	*	*			*	*						
Adverse Events Assessment	X	X				X				X			
Staging Imaging q 6wks**	X	Tumor measurements are repeated every 6 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.											X
Paraffin Embedded Tissue Collection	X												
Urine β-HCG (pregnancy test)	X												

†CMP includes Na, K, Cl, CO2, BUN, Cr, Glu, AST, ALT, ALK Phos, Bili, Ca, Phos, Total Protein, Albumin.

§ Baseline ECG (EKG) and in case of QTc prolongation, there will be follow up ECGs- see section 6.1.

*Only if Pre-Study ECG (EKG) shows a grade I QTc prolongation. See section 6.1.

**Staging will consist of cross sectional imaging with CT scan of chest, abdomen and pelvis or MRI of abdomen and pelvis with CT of the chest. The same imaging modality and technique should be used for each episode of re-imaging. Bone scan will be done at study entry: if it is negative then it need not be repeated unless symptoms, signs or other imaging suggests bone metastases. If the bone scan is positive or equivocal for metastases then it should be repeated at each imaging episode. Note: If patient remains on study therapy beyond cycle 12 then imaging can be repeated every 12 weeks for the remainder of the study in the absence of symptoms or signs suggesting progression.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be evaluated for disease at baseline prior to treatment start and then re-evaluated for response every 6 weeks (i.e. after every 2 cycles). For patients who achieve a CR or PR, the next set of scans will serve as confirmatory scans, provided that they are obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1)[45]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with eribulin and gemcitabine.

Evaluable for objective response. Eligible patients who have measurable disease present at baseline and have received any amount of protocol therapy, will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray or as ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only

the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based

evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial

responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the

baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥3 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥3 wks. Confirmation**
CR	Not evaluated	No	PR	

PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥3 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. Patients who begin another cytoreductive therapy prior to prior to progressing will be censored at the time of their last disease evaluation prior to starting the new treatment. Patients who have not yet progressed or died will be censored at the time of their last disease evaluation. Progression of disease (PD) will be defined as described above and as assessed at the local treating institution.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Study Oversight

See also Section 14 'CCCP POLICIES FOR MONITORING CONSORTIUM TRIALS,' Subsection 14.1 'Oversight.

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician through IWRS and Medidata Rave.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring

plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Read-Only, or Site Investigator) on either the Corresponding Organization or Participating Organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data is to be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/CTMS. On-site audits will be conducted on a 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at ctms@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the

provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the

guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

This is a Phase II/Screening trial. Currently there is no highly effective "standard of care" for patients with advanced urothelial cancer who are not suitable candidates for receiving cisplatin-based therapy; and in this setting, the gemcitabine-carboplatin combination (GC) is often used. Based on the results of this screening trial, if the activity of GE is sufficiently promising based on the overall response rate, then the next step would be to plan a randomized Phase II trial of GE vs. GC; if GE demonstrates superiority in terms of progression-free survival (PFS), then a Phase III study would be considered. After discussion with CTEP, it was determined that for GE to be considered sufficiently promising for further study in this population of patients with advanced urothelial cancer who are not suitable candidates for receiving cisplatin-based therapy, that GE should have a response rate that was clearly greater than 20% and not significantly less than 50%.

13.1 Study Design / Endpoints

Primary Endpoint. The primary endpoint in this trial is objective response rate defined as either a confirmed complete response (CR) or a confirmed partial response (PR) based on RECIST v1.1 (described in Section 11.1 above).

Study Design. This trial will use a Simon two-stage Optimum design, with a false-positive error rate of 9% when the true objective response rate is 20% and a false-negative error rate of 9% when the true response rate is 50%. A total of 7 patients will be enrolled in the 1st stage. The first-stage stopping rule is defined as observing only 1 or fewer responses among the first 7

patients. If 2 or more responses are observed, the trial will continue to a total of 21 patients. If 7 or more patients of the 21 experience a CR or PR then this will be evidence that the true response rate of GE is greater than 20% and not significantly less than 50%.

Study enrollment will be extended beyond 21 patients treated to 21 response-evaluable patients if the following 2 conditions hold: (1) 7 or more patients of the 21 eligible patients experience a CR or PR, AND (2) there are patients who failed to receive 2 courses of treatment and undergo radiographic evaluation of tumor burden after the 2nd course for reasons be unrelated to disease progression. Thus accrual will be extended to "replace" patients who terminated treatment early for reasons of adverse events or toxicity or decisions unrelated to disease progression; patients who fail to receive 2 courses because of early progression will not be "replaced". Although all eligible patients who begin treatment will be included in the primary analysis, this extension will permit an estimate of the response rate in those patients who could receive 2 courses of therapy. Accrual will be assessed on a quarterly basis.

Secondary Endpoints. The secondary endpoints are (1) progression free survival calculated from the date of start of GE treatment to the date of progression or death prior to progression (as defined in Section 11.1.6), and (2) toxicity as graded by the CTCAE v4**.**

Monitoring Safety/Tolerability. Safety and toxicity will be reviewed monthly at the CCCP Data Coordinating Meetings, in which all toxicities (especially Grade 3+) are assembled and reviewed. The first 7 patients treated with the combination of gemcitabine and eribulin will be specifically monitored during these calls. In addition, safety boundaries (using a modified sequential probability ratio test) will be used to flag an unexpected number of patients who experience unacceptable toxicity (TOX).

In this Phase II/screening trial, unacceptable toxicity (TOX) will be defined as any toxicity related to treatment, that results in failure to complete two courses of GE, or treatment related death at any time on treatment. Patients who have not yet completed the first 2 courses of GE, or who do not complete 2 courses of treatment and do not experience an unacceptable toxicity, will not be considered at risk for TOX (for purposes of applying these toxicity monitoring boundaries only).

Criteria for flagging an excessive number of patients with TOX are based on the sequential probability ratio test with α=0.15, β=0.10, p_o=0.10 and p_a=0.25. Every time a patient is classified as having had a TOX, the cumulative number of patients (X) who have experienced a TOX will be compared to the number of patients (N) who are at risk. If the number of patients, N, is greater than N_X, the number given in the bottom row of the Table below, then the boundary has not been crossed. If N is less than or equal to N_X, then the boundary has been crossed and a careful review of all the toxicities and tolerability will be initiated.

Table: Boundary for Monitoring Toxicity				
X: # pts who experienced a TOX	2	3	4	5
N_x: Boundary crossed if # pts. At risk (N) is ≤ N_x	≤2	≤8	≤14	≤20

These rules were selected to ensure a small chance that the boundary would not be crossed if the

true chance of TOX were less than 10% and a reasonable chance that the boundary would be crossed if the true chance were 25-30%. The Table below summarizes these probabilities. The values in the table below are based on 10,000 simulations and are accurate to ±0.01 (based on a 95% confidence interval).

Table: Probability that the Toxicity Monitoring Boundary is Crossed Because Too Many Patients Experienced a TOX					
True Chance of an Unacceptable Toxicity (TOX)	10%	15%	20%	25%	30%
Probability of Suspending Accrual to Review Toxicities	0.08	0.24	0.45	0.64	0.80

13.2 Sample Size/Accrual Rate

This trial will enroll a minimum of 7 eligible patients who begin treatment and a maximum of up to 25-29 patients, depending on how many patients will be replaced because they did not receive 2 courses.

This trial is expected to accrue patients at a rate of approximately 2 patients per month.

This study is open to men and women and to all racial and ethnic categories. Based on the accrual to our nearly completed trial of eribulin as a single agent in advanced bladder cancer (NCI # 7435), we would expect the following accrual to this trial.

Accrual Targets (for n=21)					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	0	+	2	=	2
Not Hispanic or Latino	6	+	13	=	19
Ethnic Category: Total of all subjects	6	+	15	=	21
Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	2	=	2
Black or African American	0	+	0	=	0
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	6	+	13	=	19
Racial Category: Total of all subjects	6	+	15	=	21

13.3 Stratification Factors

Not applicable in this study.

13.4 Analysis of Results

The outcome status (in terms of toxicity, number of course begun, amount of eribulin and gemcitabine received (and percent of planned), reason off treatment, tumor response, and

progression/survival) of all patients registered in this study, will be reported. All eligible patients who begin treatment will be included in the primary analysis of response and progression-free survival. All toxicities experienced by patients who begin treatment will be reported.

Toxicity. All observed toxicities will be summarized in terms of type (organ affected or laboratory determination such as absolute neutrophil count), severity (by the CTCAE v4.0), and time of onset (i.e. course of treatment). Tables will be created to summarize these toxicities and side effects, overall, by course – possibly by the cause of the cisplatin ineligibility, if numbers permit.

Clinical Outcome. The overall response rate will be calculated as the ratio of the number of eligible patients who experienced a confirmed CR or PR (by RECIST v1.1) divided by the total number of eligible patients who began treatment; 90% confidence intervals will be constructed. A secondary estimate (more conservative) of the overall response rate will count in the numerator, only those patients who experienced a confirmed CR or PR AND who received 2 or more doses of eribulin. PFS will be measured from the start of treatment on Day 1, until progression, death, or the start of another treatment; patients who have not progressed, but who begin another treatment, will be censored at that time, for the measure of PFS. This is a secondary endpoint, and will be summarized with a Kaplan-Meier plot and confidence intervals (at 3, 6, 9, and 12 months). Overall survival will also be summarized in a manner similar to PFS.

13.5 Reporting and Exclusions

Evaluation of toxicity. All toxicities experienced by patients who receive any treatment of eribulin or gemcitabine will be reported. For purposes of applying the criteria to monitor toxicity/safety, only those patients who complete the first 2 courses of treatment or who experience a TOX will be evaluable.

Evaluation of response. All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All patients who met the eligibility criteria (with the exception of those who never received any protocol treatment) will be included in the primary analysis of the response rate. Patients in response categories 3-9 are considered to be non-responders. Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

A secondary analysis of response will include only those patients who have received at least 2 doses of eribulin and had disease reassessment after the 2nd course, or who had progressive disease prior to completing 2 courses.

14. CCCP POLICIES FOR MONITORING CONSORTIUM TRIALS

The protocol principal investigator (PI) is responsible for monitoring the conduct and progress of this Phase II trial, including the ongoing review of accrual, data and toxicities, as well as the accumulation of reported adverse events from other trials testing the same drug(s). The participating clinicians and their designees are responsible for timely submission of adverse event reports (see Section 7.0) and case report forms. The Data Coordinating Center for the CCCP Consortium is responsible for providing the PI with access to the submitted case report form data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported adverse events and the impact that these have on the continued conduct of the trial, it is the Data Coordinating Center of the CCCP that distributes all submitted SAE reports to the appropriate individuals, including the local protocol principal investigators, at each of the participating institutions.

The Data Coordinating Center posts a summary (accrual, toxicities, and responses) of each CCCP initiated trial on the CCCP website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of:

(a) for Phase I trials, all dose limiting toxicities and decisions regarding dose escalation, expansion, as well as decisions to terminate escalation, and
(b) for Phase II trials, the toxicities and therapeutic endpoints referred to in the statistical plan.

The Data Coordinating Committee meets monthly to review data management and data quality issues – completeness of data submissions as well as accuracy in terms of built-in, computerized logic checks. Any issues identified and the corrective plans are presented to the Internal Committee and at the next CCCP teleconference meeting for review and approval.

14.1 Oversight

Oversight of the conduct of CCCP trials occurs at several levels:

1. The Data Coordinating Center for the CCCP flags all trials that are approaching a decision in terms of toxicity (for both Phase I and Phase II trials) or responses (for Phase II trials). Decisions are made by the PI with input from the statistician and discussion with the principal investigator of the funding mechanism (U01 Cooperative Agreement or N01 Contract, as appropriate) or his or her designee, and are communicated to the participating centers by the CCCP Data Coordinating Center. At the monthly teleconferences, the accrual of each open protocol is reviewed.

2. For CTEP sponsored Phase I trials, data are reported to the NCI-designated clinical trials monitoring service (CTMS) which will audit patients' records on each protocol – at each CCCP institution; this audit is initiated by CTEP.

3. An independent CCCP DSMC will review CCCP trials every 6 months. This DSMC will consist of 5 voting members (3 medical oncologists or hematologists involved in

Phase I/II cancer clinical trials but not participating in CCCP studies, a patient representative and a statistician) and a non-voting CCCP statistician.

a. DSMC meetings will take place twice a year. Additional meetings will be convened if necessary.
b. This DSMC will review each CCCP trial in terms of accrual, toxicity/safety, and adherence to trial design, audit results, and likelihood of successful completion.
c. The DSMC will report to the CCCP leadership.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.